Novel Quercetin-1,2,3- Triazole Hybrids using the 1,3-Dipolar Cycloaddition (Click) Reaction: synthesis and antiproliferative activity assays

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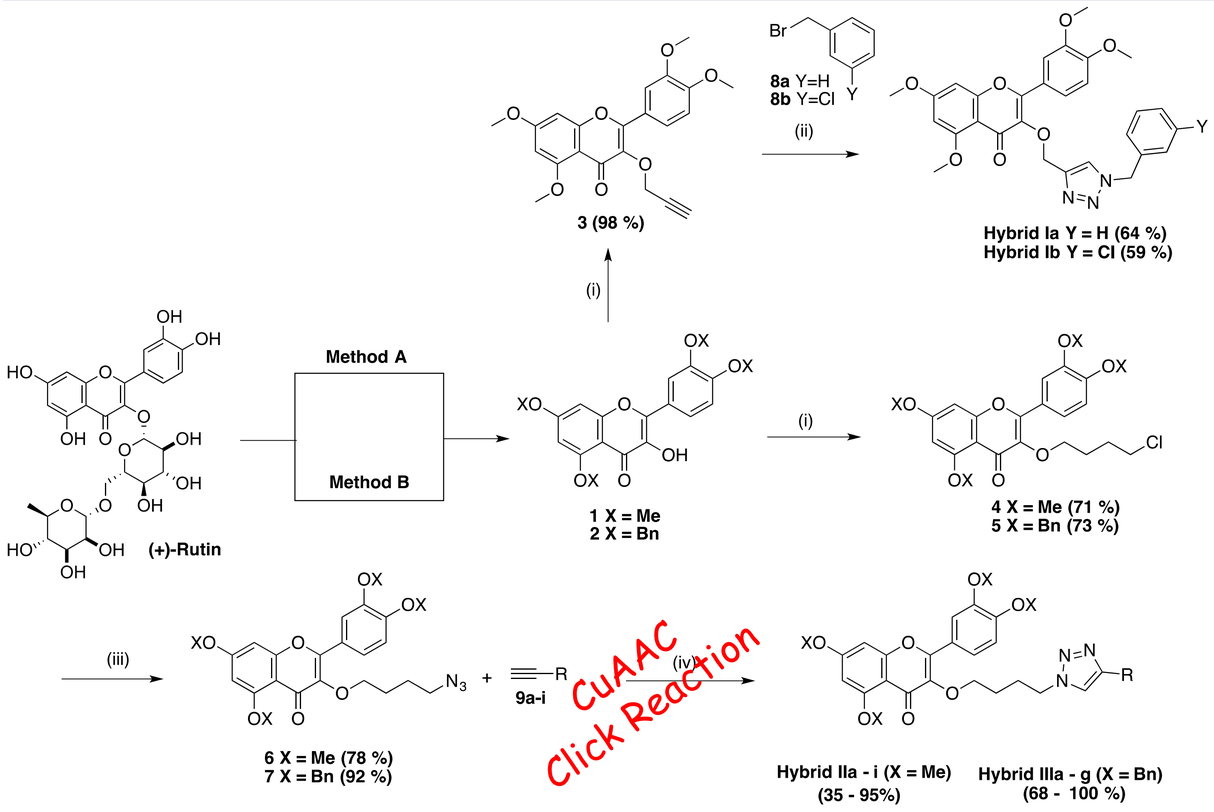
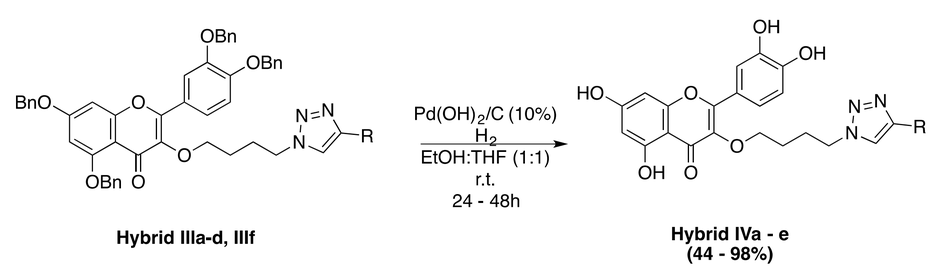
Background & Aim

Quercetin is a polyphenolic flavonoid with recognized strong antioxidant potential, which can prevent and treat several diseases. Hybrids containing a heterocyclic 1,2,3-triazole have shown promising biological properties, such as anticancer, anti-Alzheimer's, among others. The hybridization of these two entities can allow the discovery of new molecules with more potent biological properties.[1-3]

In this comunication the main goal was to synthesize four different families of 1,2,3-triazole-quercetin hybrids and evaluate their antiproliferative activity against REM-134 canine mammary cancer cell line.

Synthesis of the Quercetin-1,2,3-Triazole Hybrids I-IV





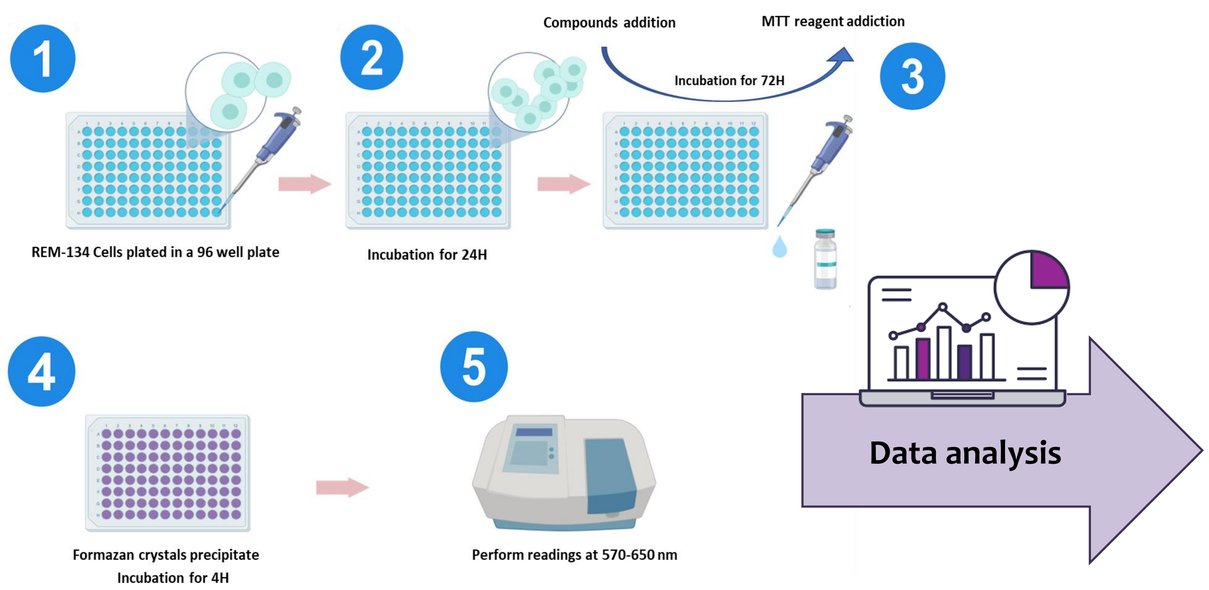
Scheme 2. Debenzylation of hybrids III via catalytic hydrogenolysis

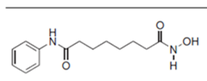
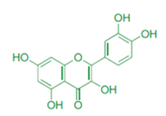
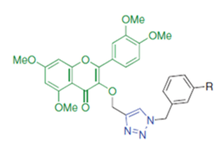
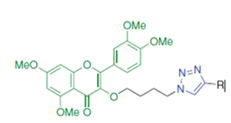
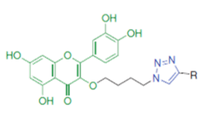
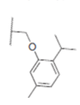
Table 1. Yields for the synthesis of hybrids **II-IV**.

Alkyne (9)	R=	Hybrid	Yield (%)	hybrid	Yield (%)	hybrid	Yield (%)
a	Phenyl	**IIa**	92	**IIIa**	100	**IVa**	98
b	cyclopropyl	**IIb**	63	**IIIb**	100	**IVb**	95
c	1-hydroxycyclopentyl	**IIc**	52	**IIIc**	100	**IVc**	92
d	1-hydroxymethyl	**IId**	90	**IIId**	96	**-**	-
e	2-hydroxypropan-2-yl	**IIe**	90	**IIIe**	98	**IVd**	65
f		**IIf**	94	**IIIf**	78	**-**	-
g		**IIg**	95	**IIIg**	68	**IVe**	42
h	propanyl	**IIh**	35	**-**	-	**-**	-
i	2-aminopropan-2-yl	**IIi**	55	**-**	-	**-**	-

Scheme 1. Synthetic route for the synthesis of hybrids I–III. Reagents and conditions: **Method A**: (a) MeI, DMF, r.t., overnight; (b) HCl 5%, reflux, 3 h.; **Method B**: (a) BnBr, DMF, r.t., overnight; (b) HCl (5% in methanol), reflux, 3 h; (i) propargyl bromide (1.5 equiv) or $Br(CH_2)_4Cl$ (1.5 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, overnight; (ii) $Cu(OAc)_2{\cdot}H_2O$ (5 mol%), sodium L-ascorbate (20 mol%), 1,10-phenanthroline (5 mol%), aryl bromides **8a–b** (1 equiv), sodium azide (1.2 equiv), $EtOH/H_2O$ (1:1), 90 °C, MW, 0.5–1 h; (iii) Sodium azide (1.5 equiv), DMF, 120 °C, MW, 1 h; (iv) $CuSO_4{\cdot}5H_2O$ (5 or 10 mol%), sodium L-ascorbate or L-ascorbic acid (20 mol%), alkyne **9a–i** (1 equiv), DMF, 90 °C, MW 0.5 h.

Antiproliferative Activity (IC_{50}, μM) against REM-134 Canine Mammary Carcinoma Cell Line



Compounds Structure	R	Code	IC_{50} (μM)
	-	SAHA	1
	-	Quer	>100
	H	**Ia**	$0.1 < IC_{50} < 10$
	Cl	**Ib**	0.62
	phenyl	**IIa**	0.12
	cyclopropyl	**IIb**	11
	1-hydroxycyclopentanyl	**IIc**	$10 < IC_{50} < 100$
	1-hydroxymethyl	**IId**	>100
	2-hydroxypropan-2-yl	**IIe**	$10 < IC_{50} < 100$
		**IIf**	0.11
		**IIg**	0.3
	propanyl	**IIh**	7.1
	2-aminopropan-2-yl	**IIi**	ca. 10
	phenyl	**IVa**	0.075
	cyclopropyl	**IVb**	0.041
	1-hydroxycyclopentanyl	**IVc**	0.16
	2-hydroxypropan-2-yl	**IVd**	>100
		**IVe**	0.18

Conclusion

The results show that some of these new quercetin-1,2,3-triazole hybrids have better activity than quercetin itself. Our best inhibitors displayed IC50 values in the range of 41–180 nM, which will be a promising contribution for treatment of both canine and human breast cancer.

Bibliography

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2. (a) Dheer, D.; Singh, V.; Shankar, R. *Bioorg. Chem.* **2017**, *71*, 30. (b) Xu, Z.; Zhao, S.-J.; Liu, Y. *Eur. J. Med. Chem.* **2019**, *183*, 1117002. (c). Carreiro, E.P. et al *Synlett* **2020**, *31*(06), 615-621.
3. Carreiro, E; Gastalho, C. et al. *Synthesis*, **2022**, *54(19)*, 4272.

Acknowledgments

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